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10/542,435	05/02/2006	Jeffrey D. Rothstein	JHU2090-1	2771

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EXAMINER	
MACFARLANE, STACEY NEE	
ART UNIT	PAPER NUMBER
1649	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,435	ROTHSTEIN ET AL.	
	Examiner	Art Unit	
	STACEY MACFARLANE	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,6,8-12 and 18-44* is/are pending in the application.

4a) Of the above claim(s) *1,5,6,8,11,12,18 and 20-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,9,10 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 7, 2009 has been entered.

Response to Amendment

2. Claims 3, 4, 7 and 13 have been canceled. Claims 2 and 9 have been amended as requested in the amendment filed on August 7, 2009. Following the amendment, claims 1, 2, 5, 6, 8-12 and 18-44 are pending in the instant application.

Claims 1, 5, 6, 8, 11, 12, 18 and 20-44 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper filed on April 17, 2007.

Claims 2, 9, 10 and 19 are under examination in the instant office action.

3. Applicant's arguments filed on August 7, 2009 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 2, 9, 10 and 19 are rejected under 35 U.S.C. 101 because the claimed invention, a screening method for identifying a compound capable of modulating the expression of a GTRAP3-18 nucleic acid or polypeptide, is not supported by either a specific and substantial asserted utility or a well-established utility.

The pending claims have been reviewed in light of the Utility Examination Guidelines 60 FR 36263 (1995) and at 1177 O.G. 146 (1995) and the Revised Utility Guidelines, Vol. 64, Number 244, December 21, 1999.

The Examiner is using the following definitions in evaluating the claims for utility.

"Specific"-A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention.

> "Substantial"-A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

"Well-established"-a specific, substantial and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material alone or taken with the knowledge of one skilled in the art.

The claims are directed to a screening method for identifying a compound which modulates cellular glycosylation comprising assaying the compound's ability to modulate the expression of GTRAP3-18.

On page 1, the specification states that the invention features screening assays for identifying modulators of cellular glycosylation and further provides for methods for treating subjects suffering from or at risk of developing "glycosylation associated disorders, particularly neurological disorders". The disclosure states that the invention is

based, at least in part, on the discovery that the glutamate transporter regulatory protein GTRAP3-18 acts as a general regulator of cellular glycosylation, including glycosylation of neurotransmitter transporters and receptors, including glutamate transporters, dopamine transporters, GABA transporters, and amino acid transporters (ASCTs) (page 3). The disclosure asserts that the utility of the invention provides methods for the identification of compounds useful in modulating cellular glycosylation as well as methods for the diagnosis and treatment of a "glycosylation associated disorder (e.g., a disorder characterized by aberrant GTRAP3-18 polypeptide activity or aberrant GTRAP3-18 nucleic acid expression, such as a neurological disorder)" (pages 3-4). The specification variously teaches other asserted utilities such as modulating (increasing or decreasing) glycosylation in a subject. None of the teachings with regard to the asserted utilities, indicate that a nexus has been established between the glycosylation and a specific disease, disorder or physiological process, which one could reasonably predict to be affected by the administration of a compound identified by the claimed method. Instead, the disclosure merely provides generic recitations of what essentially any compound identified by a screening method may be used for.

Furthermore, even if a specific utility were among those set forth in the specification, the identification and reasonable confirmation of a "real world" context of use for the screened compound would require further experimentation. The specification concludes:

> "GTRAP3-18 acts to modulate glycosylation of glutamate transporter proteins; GTRAP3-18 is an interacting protein of the EAAT family discovered by a yeast-two-hybrid screen; GTRAP3-18 is able to substantially reduce the activity of co-expressed rEAAT3, rEAAT4, and rEAAT1, rEAAT2 (rEAATs); GTRAP3-18 alters

> the apparent molecular weight of rEAATs following co-expression in HEK 293 cells. This decrease in electro-mobility is the replicated through cleavage of N-linked oligosaccharides using PNGase F; and GTRAP3-18 appears to be a reticular protein that interacts with the endoplasmic reticulum" (page 60).

The asserted function of the compound that modulates GTRAP3-18 expression is purely hypothetical and is solely based upon protein interactions between GTRAP3-18 and glutamate transporters. There is no evidence of a nexus between GTRAP3-18 expression or activity and the etiology or pathology of a specific disease, nor is there evidence that a compound that modulates GTRAP3-18 nucleic acid or protein expression would be useful to treat said specific disease or disorder. Thus, the asserted utility that the compound identified by the invention of the claims may be used as a treatment of glycosylation-associated disorders or neurological disorders, in general, does not define a either a specific utility or an immediately apparent, "real-world" utility.

Claims 2, 9, 10 and 19 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. As currently amended, Claims 2 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al. (2001) cited in the previous Office action mailed June 13, 2007.

On pages 8 of Remarks filed August 7, 2009, Applicant traverses the rejection on the grounds that "the Office Action alleges, that Lin et al. teach each of the active steps of the claimed method including contacting a neuronal cell with a test compound and assaying the ability of the test compound to modulate the expression of GTRAP3-18 protein expression and activity as determined by glutamate transport (EAAC 1) activity" (emphasis added)

Contrary to Applicant's assertions, section (b) of Claim 2 reads in the alternative:

"b) identifying the test compound as a modulator of cellular glycosylation by assaying the ability of the test compound to modulate the expression of a GTRAP3-18 nucleic acid molecule or polypeptide, OR the activity of a GTRAP3-18 polypeptide by detecting the level of glvcosvlation of a GTRAP3-18 target molecule, thereby identifying a compound which modulates cellular glycosylation." (emphasis added)

The Lin prior art teaches contacting cells expressing GTRAP3-18 with test compounds (antisense oligomers and retinoic acid) and assaying the ability of the test compounds to modulate GTRAP3-18 protein expression. Specifically, the Lin reference

teaches neuronal cells and transfected cell lines contacted with retinoic acid increase GTRAP3-18 protein expression (Figure 4a). Retinoic acid is thereby identified as a compound which modulates cellular glycosylation. Lin et al. also demonstrate that antisense GTRAP3-18 oligomers modulate, namely reduce, endogenous GTRAP3-18 expression (Figure 3d). GTRAP3-18 antisense oligomers are thereby identified as compounds which modulate cellular glycosylation. Therefore, the method of the instant claims fails to distinguish over that disclosed by the prior art.

7. Claims 2 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent 6808893 ('893 Patent) for reasons of record.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

On page 9 of Remarks filed August 7, 2009, Applicant traverses the rejection on the grounds that the Rothstein et al. prior art fails to teach a method for identifying a compound including assaying the ability of the compound to modulate the expression of a GTRAP3-18 nucleic acid molecule or polypeptide.

The '893 Rothstein Patent teaches methods comprising contacting cells with test compounds (GTRAP3-18 antisense oligonucleotides and retinoic acid) and assaying the

ability of these test compounds to reduce GTRAP3-18 protein expression. Specifically the the '893 Patent that GTRAP3-18 antisense oligonucleotides decrease GTRAP3-18 protein expression (Figure 8A-C), and states, "Retinoic acid induces a large increase in GTAP3-18 expression" (column 46, lines 40-41). Furthermore, the Rothstein Patent discloses methods specifically comprising neuronal cells expressing GTRAP3-18 (column 41, lines 5-24 and Example 11), as required by the instant claims (Claim 19). The '893 Rothstein Patent thereby identifies GTRAP3-18 antisense oligonucleotides and Retinoic acid as compounds which modulate GTRAP3-18 protein expression, thereby modulating cellular glycosylation. Thus, the method of instant claims fails to distinguish over that disclosed within the prior art.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 2, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. as applied to claims 2 and 19 above, and further in view of Hirabayashi et al. (2002).

On pages 10-11 of Remarks (Id), Applicant traverses on the grounds that Lin et al. failed to teach each of the limitations of the claims. "Applicants respectfully submit that both Lin et al. and Hirabayashi et al. are silent with respect to the correlation

between GTRAP3-118 activity regulation or expression and modulation of cellular glycosylation" (page 11). While this has been carefully considered it is not found persuasive because the active steps of the claim do not require a correlation between GTRAP3-18 expression and cellular glycosylation, but merely state that a compound identified as modulating (increasing or decreasing) GTRAP3-18 expression is thereby identified as a compound that modulates cellular glycosylation.

Lin prior art teaches a method comprising contacting neuronal cells expressing GTRAP3-18 with test compounds and assaying the ability of the compound to modulate GTRAP3-18 protein expression. The Lin et al. prior art further discloses a specific protein-protein interaction between GTRAP3-18 and EAAT1 ("EAAC1" of the reference, Figure 1). Thus, teaching that EAAT1 is a GTRAP3-18 target molecule. The Lin et al., reference further teach that the expression of GTRAP3-18 directly affects the activity of the EAAT1 glutamate transporter (Figure 3a).

The Lin reference does not teach detecting the level of glycosylation of EAAT1, the "GTRAP3-18 target molecule", as required by claim 2, part (b) after the alternative "or", and dependent claims 9 and 10. The Hirabayashi et al. reference, however, discloses that a variety of techniques (i.e. mass spectrometry, 2-D/3-D mapping and ConA-agarose column purification) for quantification of protein glycosylation were known in the art prior to filing. Specifically, Hirabayashi et al. disclose these methods are essential for a understanding the effects of glycosylation, which is "involved in numerous biological phenomena, such as cell development, differentiation, implantation, morphogenesis, tumor metastasis, microbe infection, etc." and that, in cell

culture models, mutations in the pathways of glycosylation demonstrate no altered phenotypes, whereas genetic defects in these pathways lead to termination of development at the embryonic stage (pg. 68, column 2, lines 5-13).

It would have been well within the technical skill of one of ordinary skill in the art to combine the methods of detecting modulation of glycosylation as taught by Hirabayashi et al. with the methods of testing the effects of test compounds on GTRAP3-18 expression and activity as described in Lin et al. A skilled artisan would be motivated to combine because the Hirabayashi reference explicitly teaches that quantification of glycosylation allows for a fuller investigation and the understanding of the role that glycosylation plays in normal physiology and disease conditions. Therefore, the invention as a whole is *prima facie obvious*, if not actually anticipated by the reference.

Conclusion

10. No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M-W and F 5:30 to 2, TELEWORK-Thursdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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